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RESEARCH: TREATMENT

In a cohort of individuals with type 2 diabetes using the drug sulfasalazine, HbA_{1c} lowering is associated with haematological changes

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Abstract

Objectives: Several small studies indicate the sulphonamide component of the drug sulfasalazine lowers $HbA_{1c.}$ We investigated reduction of HbA_{1c} following incident prescription of sulfasalazine and related aminosalicylates, lacking the sulphonamide group, in an observational cohort.

Research Design and Methods: Individuals in the Scottish Care Information Diabetes Collaboration (SCI-Diabetes) with type 2 diabetes and incident prescription for an aminosalicylate drug (sulfasalazine, mesalazine, olsalazine or balsalazide) were identified. Baseline and 6-month HbA_{1c} were required for eligibility, to calculate HbA_{1c} response. To investigate association with haemolysis, change in components of full blood count was assessed. Paired t-tests compared difference in baseline and treatment HbA_{1c} measures and other clinical variables.

Results: In all, 113 individuals treated with sulfasalazine and 103 with mesalazine (lacking the sulphonamide group) were eligible, with no eligible individuals treated with olsalazine or balsalazide. Baseline characteristics were similar. Mean (SD) HbA_{1c} reduction at 6 months was -9 ± 16 mmol/mol ($-0.9 \pm 1.4\%$) ($p < 0.0001$) in those taking sulfasalazine with no reduction in those taking mesalazine (2 ± 16 mmol/mol ($0.2 \pm 1.4\%$). Sulfasalazine but not mesalazine was associated with a mean (SD) increase in mean cell volume of 3.7 ± 5.6 fl ($p < 0.0001$) and decrease in red cell count of $-0.2 \pm 0.4 \times 10^{-12}$/L ($p < 0.0001$).

Conclusions: In this observational, population-based study, sulfasalazine initiation was associated with a 6-month reduction in HbA_{1c}. This correlated with haematological changes suggesting haemolytic effects of sulfasalazine. Haemolysis is proposed to contribute to HbA_{1c} lowering through the sulphonamide pharmacophore. This suggests that HbA_{1c} is not a reliable measure of glycaemia in individuals prescribed sulfasalazine.

KEYWORDS

Sulfasalazine, HbA1c, type 2 diabetes, glucose, sulphonamide, haemolysis

Samira M. S. N'Dow and Louise A. Donnelly have contributed equally to this work.

1 | INTRODUCTION

HbA_{1c} testing has a significant role in management of diabetes because it gives an average indication of glycaemic control, avoiding day-to-day variations evident in glucose monitoring.[1] In addition, HbA_{1c} is a strong predictor of risk for development of diabetes-related complications,[2] as well as being a cornerstone of glycaemic control targets and diagnosis of diabetes in national and international guidelines.[3,4] Haematological abnormalities including haemolytic anaemias, haemoglobinopathies, splenomegaly, blood loss/transfusion and chronic liver disease are known to interfere with the accuracy of the HbA_{1c} test.[5,6] However, there are few large-scale studies examining changes in HbA_{1c} following incident drug treatment. Previously, the sulphonamide drugs dapsone, sulfamethoxazole and sulfasalazine have been reported to lower HbA_{1c} in case reports and case series.[7–13] One study attributed the effect of sulfasalazine on HbA_{1c} to glucose lowering[13]; however, most other studies attribute lowering of HbA_{1c} to haematological changes in dapsone[7,8,12] and sulfasalazine-treated individuals.[7,12] Consistent with a 'false' lowering of HbA_{1c}, measures of glucose and fructosamine, which is an additional measure of long-term glucose control, were unaffected by these drugs.[7,9,11,12] Previous work suggests that even mild, subclinical haemolysis that does not produce anaemia could have significant impacts on HbA_{1c}.[7,11]

Dapsone and sulfamethoxazole are prescribed only rarely in Scotland but in contrast sulfasalazine was prescribed 112,765 times in the most recent year for which data were available, accounting for around 0.1% of all prescriptions, placing it in the top 10% of drugs prescribed[14] in a population of just over five million people. In the current study, we have compared the effects of sulfasalazine and related 5-aminosalicylate (5-ASA) drugs on HbA_{1c}. Sulfasalazine was the first ASA drug effective in inflammatory bowel disease (IBD), a term mainly used to describe Crohn's disease and ulcerative colitis. Sulfasalazine consists of 5-ASA joined with a sulphonamide group by a diazo bond (see Figure 1). The action of sulfasalazine in IBD relies on the diazo bond being cleaved in the colon, releasing the 5-ASA (reviewed in[15]). The 5-ASA component is poorly absorbed from the gastrointestinal tract, reaching its highest concentration in the colon and rectum. The sulphonamide moiety is well absorbed from the gut; systemic absorption of the sulphonamide moiety is likely to cause the classical adverse effects of sulfasalazine such as: blood dyscrasias, hypersensitivity reactions and infertility in men, as well as more common effects such as headaches and nausea.[15,16] These adverse effects often result in difficulty titrating the drug to a high enough dose for therapeutic anti-inflammatory effect of the 5-ASA.[15]

Further therapies were developed with the aim of making the therapy more targeted to avoid sulfasalazine's side effects.[17] The development of 5-ASA drugs lacking the sulphonamide group eliminated the side effects associated with sulfasalazine.[15] Oral 5-ASA on its own is not an effective therapy as the drug is not concentrated in the distal gut. Newer drugs such as mesalazine, balsalazide and olsalazine release the active compound when the drug reaches the distal small bowel area, allowing the benefits of 5-ASA in IBD without the systemic adverse side effects of sulfasalazine.[15]

The aim of this study was to analyse the association of aminosalicylate drugs sulfasalazine, mesalazine, olsalazine and balsalazide on HbA_{1c} in individuals with type 2 diabetes.

What is already known about the subject?

- In case reports and case series, sulphonamide-based drugs (including sulfa-antibiotics and dapsone) have been associated with reduction of $HbA_{1c.}$
- Haemolytic effects of the drugs have been suggested to underlie this effect.

What has this study found?

- Sulfasalazine is associated with HbA_{1c} lowering.
- This effect is correlated with haematological changes consistent with haemolysis.

What are the clinical implications of the study?

- HbA_{1c} may not be a reliable marker of glycaemia in individuals using drugs which cause haemolysis. These groups may need to employ different glycaemic monitoring tools to prevent diabetes-related complications. In these patients, HbA_{1c} may not be a reliable diagnostic tool in type 2 diabetes.

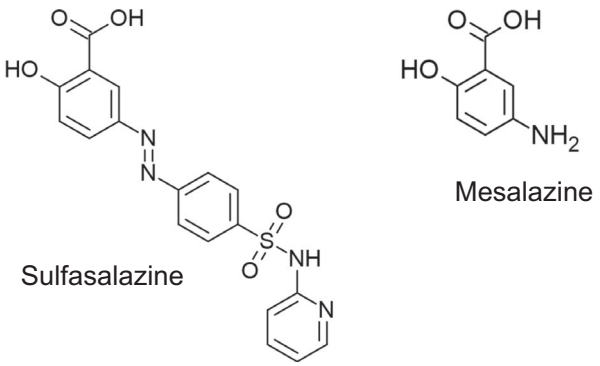

FIGURE 1 Structure of sulfasalazine molecule in comparison to mesalazine molecule.[24] Demonstrates the difference between these two drugs, in particular the sulphonamide, which in sulfasalazine only is attached with a diazo bond to the aminosalicylate moiety common to both drugs

Based on previous case report/series evidence, we hypothesised that sulfasalazine but not mesalazine, olsalazine or balsalazide, would lower HbA_{1c}. In addition, we investigated the effect of these drugs on markers of haemolysis, including full blood count–red blood cells (RBC), mean cell haemoglobin (MCH) and haematocrit (HCT).

2 | MATERIALS AND METHODS

2.1 | Data source & linkage

An observational cohort study was performed using comprehensive electronic medical records. Individuals with type 2 diabetes in Tayside and Fife were identified from The Scottish Care Information-Diabetes Collaboration (SCI-Diabetes) and linked to clinical, laboratory and encashed prescription datasets. Data were collected and integrated by the Healthcare Informatics Centre (HIC) of University of Dundee, conforming to ISO27001. This is a HIC project using anonymised data in line with HIC standard operating procedures and has Caldicott approval. Data linkage was through the Community Health Index number which is used widely in the NHS with over 99% accuracy for individuals with diabetes in Scotland.

2.2 | Study population

Complete prescribing data for aminosalicylates (defined as British National Formulary chapter 1.5.1) were available from 1st January 2005 and 1st January 2009, in Tayside and Fife, respectively, until 30th April 2017. All users of sulfasalazine, mesalazine, balsalazide and/ or olsalazine within the study period were identified. To be eligible for the study, all individuals must have received no prescriptions for aminosalicylates in the calendar year 2005 and 2009 for Tayside and Fife, respectively, and could thus be considered treatment naïve. Individuals whose first prescription was prior to diabetes diagnosis were also excluded. Therefore, the study population was defined as individuals with an incident prescription (a first prescription occurring in the specified time period) of sulfasalazine, mesalazine, balsalazide and/ or olsalazine on or after 1st January 2006 in Tayside or 1st January 2010 in Fife and after diagnosis of type 2 diabetes.

2.3 | Definition of HbA_{1c} response and other clinical variables

Baseline HbA_{1c} was defined as closest measure between 6 months prior and 7 days after drug start date. The 6-month treatment HbA_{1c} measure was defined as the measure closest to 6 months after drug start date but within a 3- to 9-month window. Although results are largely focused on 6-month response, a 1-year treatment HbA_{1c} measure was also defined as the measure closest to 1 year after drug start date but within a 9- to 15-month window. HbA_{1c} response was calculated as the difference between the baseline and treatment HbA_{1c}. For inclusion in the study, individuals were required to have a baseline and treatment measure to allow response to be assessed.

Baseline BMI, biochemical and haematological variables were defined as the closest measure between 1 year prior and 7 days after drug start date. Treatment BMI, biochemical and haematological variables were defined as measures closest to 6 months in a 3- to 12-month window. These results were solely examined for a 6-month response. Individuals were required to have both a baseline and treatment measure for the stated variables, allowing for change in study period to be assessed.

2.4 | Study population derivation

A detailed flow chart of the study population is presented in Figure 2. There were 1046 individuals with an incident 5-ASA prescription during the study period; 523 individuals treated with sulfasalazine, 506 treated with mesalazine, 53 treated with balsalazide and 11 treated with olsalazine (some individuals had prescriptions for more than one of the drugs during the study period, hence the total is 1093).

A total of 305 and 255 individuals were eligible for analysis in the sulfasalazine and mesalazine groups, respectively. Due to very small numbers in the olsalazine and balsalazide groups, these drugs were excluded from the study. Of the 305 individuals in the sulfasalazine group, 113 (37%) had a baseline and 6-month HbA_{1c} measure, and of the 255 individuals in the mesalazine group, 103 (40%) had a baseline and 6-month HbA_{1c} measure.

2.5 | Covariates

Individual characteristics of interest at baseline were gender, health board (Fife or Tayside), age at first prescription, age at type 2 diabetes diagnosis, HbA_{1c}, BMI, bilirubin, RBC, MCH, HCT, haemoglobin (Hb) and mean cell corpuscular volume (MCV).

2.6 | Co-prescribing

Co-prescribed drugs which could alter HbA_{1c} were identified from an initial list of all co-prescribed drugs. These drugs included hydroxychloroquine, opiates, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, folic acid, iron supplements and diabetes treatment.

FIGURE 2 Schematic flow chart demonstrating derivation of study population. The number of included is illustrated in each box, with number excluded represented with the arrows

2.7 | Anaemia definition

Mild anaemia was defined as haemoglobin below 12 g/dl for women and below 13 g/dl for men, and moderate anaemia was defined as below 11 g/dl for both men and women, based on World Health Organisation (WHO) definitions.

2.8 | Statistical analyses

Comparisons of baseline characteristics and co-prescribing frequency by drug group were by t-test for continuous variables and Chi-square test for categorical variables.

Paired t-tests were used to compare the difference in baseline and treatment measures of HbA_{1c} and other clinical variables. All analyses were performed using SAS 9.4 and a p value of <0.05 considered statistically significant. No adjustment was made for multiplicity of statistical tests. Scatter graphs and Pearson correlation coefficients were used to identify linear relationships between significant haematological changes (MCV, MCH, RBC) and HbA_{1c} change at 6 months.

2.9 | Sensitivity analyses

Individuals in the sulfasalazine group taking relevant co-prescribed drugs and anaemic individuals were removed from the study population and the HbA_{1C} results re-analysed. In addition, statistically significant changes in haematological variables were analysed for any correlation with HbA_{1c} response.

3 | RESULTS

3.1 | Baseline characteristics of the sulfasalazine and control group

There were a total of 113 eligible individuals in the sulfasalazine group and 103 in the mesalazine group (control group). A comparison of the two drug groups at baseline is presented in Table 1. Importantly, there was no statistically significant difference between the groups in baseline HbA_{1c} or any of the variables tested.

The frequency of drugs co-prescribed during the study period that may affect HbA_{1c} are presented in Table 2. Drugs exhibiting statistically significant differences in prescribing between drug groups were as follows: methotrexate, hydroxychloroquine, opiates, non-steroidal anti-inflammatory drugs and folic acid, which were each prescribed more commonly in the sulfasalazine cohort. The sulfasalazine group were prescribed less anti-diabetic drugs with 50% on diet or monotherapy treatment compared with 30% of the mesalazine group.

3.2 | HbA_{1c} response and haematological responses in the sulfasalazine group

Initiation of sulfasalazine was associated with a mean (SD) HbA_{1c} reduction of −9 ± 16 mmol/mol (−0.9 ± 1.4%) ($p < 0.0001$) in a 6-month period (Table 3). HbA_{1c} remained lowered by −6 ± 16 mmol/mol (−0.5 ± 1.5%) ($p = 0.004$) after 1 year. In contrast, initiation of mesalazine was associated with a non-significant increase in HbA_{1c} by 2 ± 16 mmol/mol (−0.2 ± 1.4%) ($p = 0.23$). HbA_{1c} response 1 year from incident mesalazine prescription was 0 ± 18 mmol/mol (0 ± 1.6%) ($p = 0.99$). Other statistically significant changes in the sulfasalazine group were decreased RBC and increased

TABLE 1 Comparison of baseline characteristics. Data are mean (SD) or N(%); Comparisons are by t-test for continuous variables and Chi-square test for categorical variables

Variable	Sulfasalazine		N	Mesalazine		N	p Value
Gender	Men	Women	113	Men	Women	103	0.14
	59 *(52%)*	54 *(48%)*		64 *(62%)*	39 *(38%)*		
Location	Fife	Tayside	113	Fife	Tayside	103	0.41
	49 *(43%)*	64 *(57%)*		39 *(38%)*	64 *(62%)*		
Age (years)	66.4 ± 11.5		113	65.6 ± 12.5		103	0.61
Age at type 2 diabetes diagnosis (years)	58.0 ± 12.2		113	58.2 ± 12.7		103	0.93
HbA1c (mmol/mol/%)	57 ± 17 *(7.4 ± 1.6)*		113	61 ± 18 *(7.7 ± 1.6)*		103	0.16
BMI (kg/m^2)	32.3 ± 6.5		105	31.6 ± 6.4		97	0.45
Bilirubin (μmol/L)	7.8 ± 5.4		111	8.9 ± 4.7		103	0.14
RBC (×10^{12}/L)	4.4 ± 0.5		112	4.4 ± 0.6		97	0.49
MCH (pg)	29.2 ± 2.4		112	29.7 ± 2.3		97	0.05
HCT (L/L)	0.4 ± 0.04		112	0.4 ± 0.05		97	0.29
Hb (g/dl)	12.8 ± 1.6		112	13.2 ± 2.0		97	0.06
MCV(fl)	90.4 ± 6.2		112	90.9 ± 5.3		96	0.56
Mild anaemia	50 (45%)		112	35 (36%)		97	0.21
Moderate anaemia	15 (13%)		112	13 (13%)		97	0.99

Percentages are presented in italics.

TABLE 2 Comparison of frequency of co-prescribed drugs. Data are n(%). Comparison is by chi-square test

Drug group	Sulfasalazine ($n = 113$)	Mesalazine ($n = 103$)	p Value
Hydroxychloroquine	40 *(35%)*	0 *(0%)*	<0.0001
Opiates	100 *(88%)*	66 *(64%)*	<0.0001
Steroids	51*(45%)*	41 *(40%)*	0.43
NSAIDs	50 *(44%)*	16 *(16%)*	<0.0001
Methotrexate	61*(54%)*	1 *(1%)*	<0.0001
Folic Acid	62 *(55%)*	6 *(6%)*	<0.0001
Iron Supplements	29 *(26%)*	27 *(26%)*	0.89
Anti-diabetic therapy group:			
Diet treated	25 *(22%)*	16 *(16%)*	0.02
Monotherapy	32 *(28%)*	15 *(15%)*	
Dual therapy	37 *(33%)*	44 *(43%)*	
Insulin therapy	19 *(17%)*	28 *(27%)*	

Percentages are presented in italics.

MCH and MCV levels. There were no significant changes in the mesalazine group. Figure 3 demonstrates the correlation observed between these haematological factors and the HbA_{1c} response. The HbA_{1c} response was correlated with significantly increased MCV ($p = 0.01$) and significantly decreased RBC ($p = 0.01$). A non-statistically significant correlation with decreasing MCH ($p = 0.13$) was also observed.

3.3 | Impact of co-prescribing and anaemia

We performed sensitivity analyses on the sulfasalazine group, with individuals on specific co-prescribed drugs excluded (Table 4). The lowering effect of sulfasalazine on HbA_{1c} was still evident despite the removal of these individuals. Further sensitivity analysis excluded anaemic individuals from the cohort (Table 5). This also had little impact on the HbA_{1c} response.

4 | DISCUSSION

4.1 | Principal findings

In this study, we analysed data from 216 individuals with type 2 diabetes, to study effects of the sulphonamide group of the drug sulfasalazine on HbA_{1c}. Mesalazine acted as a control, as it lacks a sulphonamide group. There was no significant difference in baseline measurements including HbA_{1c} between the two groups. The principal finding is that sulfasalazine introduction was associated with a statistically significant and clinically important decrease in HbA_{1c}, while mesalazine introduction was not. This finding suggests that the effect in the sulfasalazine-treated group depends on the systemically available sulphonamide moiety, which is absent in mesalazine, rather than being an effect of the gut-confined 5-ASA. The HbA_{1c} reduction was still evident in sensitivity analyses which excluded possible effects of co-prescribed drugs, including diabetes medications.

Our study suggests that haemolysis mediates the effect of sulfasalazine on HbA_{1c}. Haemolysis is a known adverse effect of sulphonamide drugs.[18,19] Sulphonamide-induced haemolysis was first described in the early 1900 s.[18] Significantly increased MCV, MCH and a significantly decreased RBC with incident sulfasalazine treatment are suggestive of macrocytosis[20] and possibly mild haemolysis. These changes were correlated with HbA_{1c} lowering (as shown in Figure 3), suggesting that they may be mechanistically linked. Haemolysis

TABLE 3 Changes in clinical measurements during the study period. Data are mean (SD) from paired t-tests comparing treatment – baseline measurement

	Sulfasalazine			Mesalazine		
	N	Variable change	*p Value*	*N*	Variable change	*p Value*
6 month HbA1c change (mmol/mol/%)	113	−9 ± 16 *(−0.9 ± 1.4)*	<0.0001	103	+2 ± 16 *(+0.2 ± 1.4)*	0.23
One year HbA1c change (mmol/mol/%)	72	−6 ± 16 *(−0.5 ± 1.5)*	0.004	79	0 ± 18 *(0 ± 1.6)*	0.99
BMI (kg/m^2)	94	−0.3 ± 2.0	0.13	83	−0.2 ± 1.8	0.46
Bilirubin (μmol/L)	111	−0.2 ± 5.7	0.70	101	+0.4 ± 3.2	0.21
RBC ($x10^{12}/L$)	112	−0.2 ± 0.4	<0.0001	97	+0.04 ± 0.4	0.29
MCH (pg)	112	+1.2 ± 2.1	<0.0001	95	−0.2 ± 1.6	0.35
HCT (L/L)	112	−0.01 ± 0.04	0.15	95	+0.003 ± 0.04	0.42
Hb (g/dL)	112	−0.2 ± 1.3	0.21	95	+0.03 ± 1.3	0.79
MCV (fL)	112	+3.7 ± 5.6	<0.0001	94	−0.2 ± 4.2	0.72

Percentages are presented in italics.

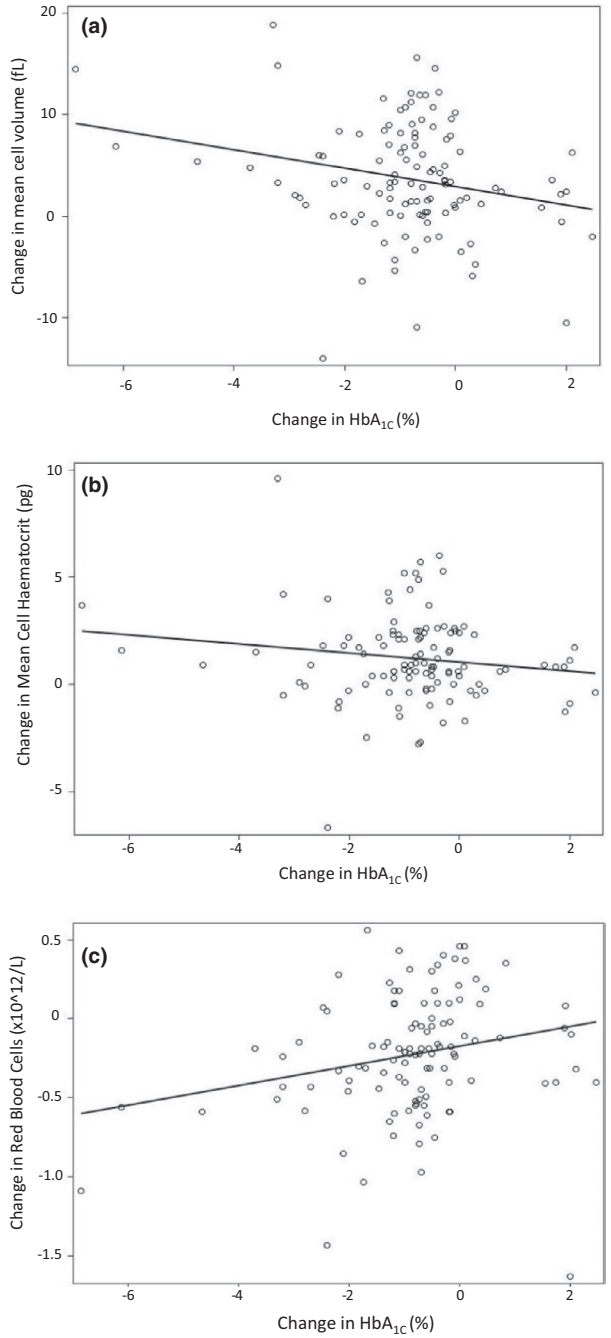

FIGURE 3 Correlations between haematological variables and HbA_{1c}. (A) Negative linear relationship between change of MCV and change in HbA_{1c} (correlation coefficient −0.23 ($p = 0.01$)); (B) Negative linear relationship between change in MCH and change in HbA_{1c} (correlation coefficient −0.14 ($p = 0.13$)); (C) Positive linear relationship between change in RBC and change in HbA_{1c} (correlation coefficient 0.23 ($p = 0.01$))

may lower HbA_{1c} by shortening lifespan of red blood cells. With an increase in red blood cell turnover, the period of time which the haemoglobin is exposed to blood glucose will be shorter, reducing the degree of glycation. This presents a possible limitation of HbA_{1c} as a glycaemic control marker in this cohort of people, as well as suggesting that HbA_{1c} is not

TABLE 4 Changes in 6 month HbA1c in sulfasalazine group with individuals coprescribed specific drugs excluded. Data are mean (SD) from paired t-tests comparing treatment – baseline measurement drugs

Drug group excluded	*N*	HbA1c response (mmol/mol/%)	*p* value
Hydroxychloroquine	73	−8 ± 13 *(−0.7 ± 1.2)*	<0.0001
Methotrexate	52	−9 ± 13 *(−0.8 ± 1.2)*	<0.0001
Folic acid	51	−9 ± 13 *(−0.8 ± 1.2)*	<0.0001
NSAIDs	63	−10 ± 18 *(−0.9 ± 1.7)*	<0.0001
Opiates	13	−17 ± 20 *(−1.6 ± 1.8)*	0.01
Steroids	62	−6 ± 12 *(−0.6 ± 1.1)*	0.0002
Iron supplements	84	−9 ± 15 *(−0.8 ± 1.4)*	<0.0001
Anti-diabetics	25	−7 ± 6 *(−0.6 ± 0.5)*	<0.0001

Percentages are presented in italics.

TABLE 5 Changes in 6-month HbA1c in sulfasalazine group with individuals with anaemia excluded. Data are mean (SD) from paired t-tests comparing treatment – baseline measurement

Level of anaemia excluded	*N*	HbA1c response (mmol/mol/%)	*p* value
Mild[a]	62	−9 ± 15 *(−0.8 ± 1.4)*	<0.0001
Moderate[b]	97	−10 ± 16 *(−0.9 ± 1.5)*	<0.0001

Percentages are presented in italics.

[a]Mild anaemia was defined as haemoglobin below 12g/dL for women and below 13g/dL for men.

[b]Moderate anaemia was defined as below 11g/dL for both men and women.

a reliable diagnostic tool in individuals taking sulfasalazine. Consistent with sulfasalazine inducing only a mild, subclinical level of haemolysis,[21] we did not detect an increase in the bilirubin levels in the blood, nor was there any significant change in haemoglobin levels. There is a well-established link between sulfasalazine use and megaloblastic anaemia,[16] which is associated with a decrease in cell turnover, allowing the red cell to have an increased exposure time to circulating glucose and ultimately *increasing* glycation of haemoglobin.[6] We investigated the possibility that megaloblastic anaemia could have masked an even more profound HbA_{1c} effect in the sulfasalazine group but in sensitivity analysis, anaemia did not have a significant impact on the effect of sulfasalazine on HbA_{1c}.

Further work will be required to determine whether other sulphonamide drugs, particularly those which are very commonly prescribed, such as furosemide, elicit similar effects on HbA_{1c}. In addition, other drugs with different structure are known to affect haematological components[22] and some of these, such as thiazides, are commonly prescribed as well; however, there has been little investigation of effects of these drugs on the HbA_{1c} test either. Alongside the suggestion that subtle abnormalities of red cells (with or without anaemia, through various mechanisms) are enough to have a significant impact on HbA_{1c},[23] further work should examine in depth the link between red cell component abnormality and HbA_{1c}.

4.2 | Limitations of this study

Our study was observational and consequently we cannot exclude that differences between the drug groups may owe to individual characteristics, particularly their disease profile. Mesalazine is prescribed only in IBD, whereas the systemic anti-inflammatory effects of sulfasalazine have led to its use in rheumatoid arthritis as well. In addition, there were some factors that this study could not account for, such as effects of short-term inflammatory or comorbid conditions, subsequent hospital admissions, medication compliance and their effects on HbA_{1c}. The study was also limited to the data available; therefore, some factors could not be analysed. These factors could have helped us to study the mechanism behind the sulfasalazine effect on HbA_{1c} further, they include vitamin B12 and folate levels, insulin, C-peptide and other markers of haemolysis such as reticulocyte count, lactate dehydrogenase and haptoglobin. In addition, oral glucose tolerance testing, fasting plasma glucose levels and fructosamine measurements were not available as alternative measures of short-term and long-term glucose control.

Despite these limitations, baseline characteristics were broadly similar between the cohorts suggestive of minimal ascertainment bias, and the use of sensitivity analyses also found little evidence of other confounding factors that could have had an influence on the final HbA_{1c} response.

We do not exclude possible mechanisms other than haemolysis underlying the effect of sulfasalazine on HbA_{1c}. Sulphonamides are structurally reminiscent, for example, of sulfonylureas and some evidence suggests they may induce insulin secretion.[24]

5 | SUMMARY

In conclusion, we have used analysis of a cohort of individuals with type 2 diabetes in Tayside and Fife to replicate at a population level, evidence from several much smaller studies suggesting that sulfasalazine mediates a clinically relevant suppression of HbA_{1c}. The effect of sulfasalazine on HbA_{1c} is likely to be mediated by the sulphonamide moiety of the drug, through a mechanism involving haemolysis. These findings suggest that HbA_{1c} is not a reliable measure of glycaemia and therefore should not be used for diagnosis and monitoring of type 2 diabetes in individuals prescribed sulfasalazine.

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